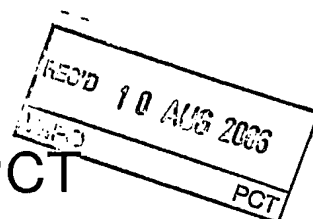


PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT



To:

see form PCT/ISA/220

P708

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2005/041252

International filing date (day/month/year)
16.11.2005

Priority date (day/month/year)
17.11.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/20 A61K31/505 A61P3/00

Applicant
BIOMARIN PHARMACEUTICAL INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Uhl, M

Telephone No. +49 89 2399-8654



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/041252

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/041252

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------|
| Novelty (N) | Yes: Claims | 1-48 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-48 |
| | No: Claims | |
| Industrial applicability (IA) | Yes: Claims | 1-48 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

Reference is made to the following document/s/:

D1: WO 2005/065018 21 July 2005

D2: EP-A-0 906 913 7 April 1999

D3: PATENT ABSTRACTS OF JAPAN vol. 013, no. 079 (C-571), 22 February 1989
(1989-02-22) & JP 63 267781 A (SUNTORY LTD), 4 November 1988

D4: ELZAOUK LINA ET AL: "Dwarfism and low insulin-like growth factor-1 due to
dopamine depletion in Pts-/- mice rescued by feeding neurotransmitter precursors
and H4-biopterin." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 30, 25
July 2003 (2003-07-25), pages 28303-28311, XP002392001 ISSN: 0021-9258
(citations see international search report)

Concerning D1 see below.

In view of D2-D4 the subject matter of claims 1-48 is novel over the prior art (Art. 33(2)
PCT).

Closest prior art is D4, where the information is verified, that closest prior art tablets as
sold by Schircks Laboratories comprise 50mg BH4, 50mg Ascorbic acid and 25 mg N-
acetyl-L-cysteine. These tablets have a shelf life of only 2 month, where 99% of the activity
is still present whereas the presently claimed tablets based on polymorph B of
tetrahydropteridin derivative have a 6month stability at ambient temperatures and 60%
humidity of 6 month. This is taken as an indication that the BH4 in the prior art tablet is not
of polymorph B form. There is no hint in the documents D2 or D3 to select this specific
polymorph form B in order to formulate a stable tablet of BH4, a problem seen since long
in the prior art.

Re Item VI

D1 will be relevant in a number of contracting states and/or regions, like the EPO, where
intermediate documents can be cited under novelty.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/041252

Claim 1 (and dependent claims 2 and 3) let open whether a excipient is used and thus encompasses tablets which only contain the active agent. In such case the high stability of the polymorph crystal form B, which is already known from D1 could be applied to the tablet as well. D1 also mentions that in particular the hydrated form D and the form B are in particular suitable for the formulation of stable oral dosage forms and tablets are explicitly listed in this connection. Certainly no specific tablets are disclosed in D1, which is the reason that it is only cited with respect to claim 1 (and the direct dependent claims 2 and 3) of the application.